



When it's time for a change: Failures to track context in schizophrenia

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ARTICLE INFO

Article history:

Received 3 April 2010

Received in revised form 5 May 2010

Accepted 13 May 2010

Available online 24 May 2010

Keywords:

P300

Schizophrenia

Context

ABSTRACT

Introduction: Reduction of P300 event-related potential amplitude in schizophrenia is perhaps the most replicated biological reflection of the illness. P300 is typically elicited by infrequent deviant events that are imbedded in a series of identical frequent standard events. Deviants have features that explicitly distinguish them from standards, whereas standards can be distinguished from each other based on their local sequential probabilities within the stimulus series. The improbable occurrence of a standard should generate a P300, but only if the implicit local context generated by the recent stimulus history is processed.

Method: To assess the ability of schizophrenia patients to process this implicit contextual information, ERPs were elicited from 22 controls and 16 schizophrenia patients during an auditory oddball task containing infrequent target tones (15%) and novel distracter sounds (15%) imbedded pseudo-randomly in a series of standard tones (70%). Consecutively presented standards following deviant stimuli varied in sequential probability from $p = 1.0$ for the 1st standard to $p = 0.16$ for the 4th consecutive standard.

Results: Patients compared to controls demonstrated smaller P300 (P3a) to the fourth consecutive standard. However, in controls but not patients a contingent negative variation (CNV) was observed prior to the fourth standard, and an N2b/mismatch negativity (MMN) was observed following it.

Conclusions: These outcomes suggest that patients are deficient in using the implicit context established by recent stimulus history to anticipate that an otherwise standard stimulus was unlikely and its occurrence unexpected.

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1. Introduction

Since Roth and Cannon (1972) first reported P300 amplitude reductions in patients with schizophrenia, more than a hundred replications and extensions of that finding have been published. Indeed, P300 amplitude reduction in schizophrenia is arguably the most replicated biological finding in the illness (Bramon et al., 2004; Ford, 1999; Jeon and Polich, 2003). To understand why P300 amplitude is reduced in schizophrenia, we need to understand the conditions responsible for its generation. Below, we describe how abnormalities in context processing may contribute to P300 reduction in schizophrenia. We explain how isolating the role of context is challenging when deviance depends not only on improbability, but also on physical deviance and task relevance. We demonstrate how context-building depends on processing of standard events, and show that a non-target, frequent standard can elicit a P300. That is, we show that a P300 can be elicited “automatically” by a stimulus that derives

its “deviance” implicitly and exclusively from local sequential probabilities, rather than from a combination of distinctive physical characteristics, task relevance, and global improbability.

1.1. P300 and task relevance

Task-relevant, target stimuli elicit a P300. While “task-relevant” and “target” stimuli are often equated, they are not the same. This was illustrated by Duncan-Johnson and Donchin (1977) and can be seen in Fig. 1a of their report. In their paradigm, subjects were presented with oddball sequences of two tones spanning a range of probabilities. These sequences were presented in two different conditions. In the Attend Condition, subjects were required to count the tone designated as the target. In the Ignore Condition, they were told to ignore all the tones and perform a distraction task. During the Ignore Condition, irrelevant tones did not elicit a P300, regardless of how improbable. In the Attend Condition, target tones elicited a larger P300 than non-target tones presented at the same level of probability, but even non-target tones elicited a P300 when they were infrequent. Thus, provided that the stimulus stream is attended to, both target and non-target stimuli are task-relevant.

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While the target status of a stimulus is essential to the elicitation of the parietally maximal P300 (also called “P3b”), a large, robust fronto-centrally maximal P300 (also called “P3a”) is generated by infrequent distractor, novel or otherwise salient stimuli with no target value (Squires et al., 1975). It has been suggested that P3a is, in fact, a reflection of the orienting response (Roth and Kopell, 1973). Indeed, it may be salience, rather than novelty, that elicits P3a as large changes in pitch (Katayama and Polich, 1998) elicit a P3a, as does a startling noise (Putnam and Roth, 1987), although neither is novel. It is critical to note that by using tools such as independent components analysis (ICA) and principle components analysis (PCA), it is possible to find evidence of both a P3a and a P3b to both targets and novel events (Spencer et al., 2001).

Importantly, patients with schizophrenia show equivalent deficits in P3a and P3b amplitude relative to healthy controls (Mathalon et al., 2000, 2010b; Pfefferbaum et al., 1989). Moreover, target events do not produce a larger group effect than novel events (Mathalon et al., 2010b). That is, the additional influence of “target value” does not affect the group difference in P300. The common denominator of target and novel events is that they both are physically deviant and improbable relative to the series of frequent standard stimuli in which they are imbedded.

1.2. P300 and probability

Another important factor in P300 generation is stimulus probability (Johnson, 1986). This was demonstrated by comparing P300s to high and low pitched tones where the probabilities of each were systematically varied between $p=0.1$ to 0.9 ; less probable tones elicited larger P300s (Duncan-Johnson and Donchin, 1977). While probability is an objective metric of the likelihood that an event will occur, other variables affect the subjective appreciation of probability, and hence the amplitude of P300 (P3b). For example, when subjects were told that the next event was a low probability stimulus, it elicited a smaller P3b than when there was some uncertainty about its occurrence (Tueting et al., 1970). That is, when a low probability event is *certain* to occur, it will elicit a smaller P300 than when its occurrence is uncertain or surprising.

Subjective probability of the occurrence of an event is determined by its global probability, as well as its local conditional probability, determined by the immediately preceding sequences of events [(Johnson and Donchin, 1982; Squires et al., 1976); Fig. 3]. These variables are also related to “surprise”, a construct that has also been used to explain variations in P300 amplitude (Donchin, 1981; Duncan-Johnson and Donchin, 1980). While the amount of surprise will depend on local and global probabilities, surprise will also vary with how subjects have incorporated that information into their expectations for one event or another.¹

Differential sensitivity to probability and expectancy could play a critical role in P300 reduction seen in patients relative to controls, however there is little evidence to support it. For example, in spite of overall reductions in P300 in a traditional oddball paradigm, patients responded normally to fluctuations in local probability (Duncan-Johnson et al., 1984). Nevertheless, there is some electrophysiological evidence that P300 reduction seen in schizophrenia may be due to failures in context updating. It is based on data showing *normal* P300s when there are *no* demands on context processing. For example, patients have normal P300s to target sounds presented at long inter-stimulus intervals (ISI), either when no standards are interposed between targets (Roth et al., 1991), or when the ISIs are so long that both standards and targets elicit similar P300 amplitudes (Mathalon et al., 2002). Similarly, we reported a normal P3a in patients using

startling noises with no target value, when there were no standards interposed between the noises (Ford et al., 1999). Notably, the same startling noises, with standards interposed between them, elicited a smaller P3a in patients than in healthy controls (Pfefferbaum et al., 1989). It was suggested that when no comparisons can be made against standards, either because there are none or because long ISIs have rendered standards as temporally unexpected and salient as targets, minimal demands are placed on context updating (Ford, 1999), a variable posited to be critical for the elicitation of a P300 (Donchin and Coles, 1988). Perhaps when demands to update context are minimal, P300 is normal in patients.

Indeed, the presence of standards seems to be key in setting the context and producing P300 reduction in schizophrenia. Although they interpreted their data in terms of neural recovery period differences, Gonsalvez et al. (1995) reported normal P300s in patients when 1 or 9 standards were interposed between targets. Perhaps both patients and controls lose track of 9 standards, and when there is only 1 standard, keeping track of it is not a problem. P300 reductions in patients were seen only when there were 3, 5 or 7 standards between targets. In this range, it appears that patients were deficient in processing the stimulus context created by the runs of standards, making deviants relatively less improbable to them and less likely to elicit a P300.

One problem with trying to elucidate the role of context processing deficits in P300 amplitude reduction in schizophrenia is that the response to deviant target or novel stimuli depends not only on the context established by the probability and local sequence of intervening standard stimuli, but also on the physical features that distinguish deviants from standards. Deficient processing of the physical features that render a stimulus deviant may contribute to P300 reduction in schizophrenia, and these effects are difficult to disentangle from context processing deficiencies. Examination of otherwise standard stimuli that derive their deviance solely from local sequential probabilities may provide a means for examining implicit context processing deficits and their role in producing P300 reductions in patients.

1.3. ERPs to standard stimuli

Brain responses to standard events may provide insight into how subjects update context. While it is common to average together brain responses to all standards, or not to process them at all, information about context processing can be gleaned from the brain's response to the standard event based on its position in the sequence. In healthy subjects, Gilmore et al. (2005) found greater parietal activity around 250 ms in response to standard stimuli the later they appeared in a sequence of consecutive standards following a target stimulus. They suggested that after a long series of identical standard tones, subjects expect a change, and when it does not occur, they are surprised. Similarly, Stadler et al. (2006) reported a parametric increase in P300 to standards as they became increasingly improbable following a target stimulus. Consistent with the idea that successive standards were associated with an increasing expectation that the next stimulus would be a target that required a button press response, Stadler et al. also observed a contingent negative variation (CNV) preceding standard stimuli when the local sequential probability indicated that a target was possible. Interestingly, the CNV amplitude was small when target probability was low, and large when the occurrence of a target was possible, regardless of its probability. This was in contrast to the P300 amplitude, which varied continuously and inversely with stimulus probability.

1.4. CNV, response preparation, and stimulus anticipation

The CNV was originally described as a negative going variation in voltage between a warning stimulus and an imperative stimulus, in a

¹ Although not directly relevant to this paper, it is worth mentioning that expectancy is also affected by temporal probability: the longer the temporal interval between targets, the larger the P300 to the target (Gonsalvez and Polich, 2002).

warned reaction time paradigm, when the probability of making a motor response was likely. The CNV is sensitive to expectancy. In fact, it was originally referred to as the E-wave, or expectancy wave (Walter, 1964). Subsequent perspectives on the CNV consider it to be a complex wave comprising an orienting response to the warning stimulus, and response preparation component and a stimulus anticipation component to the imperative stimulus (Brunia and van Boxtel, 2001; Loveless and Sanford, 1974; Rohrbaugh et al., 1976; van Boxtel and Brunia, 1994). The anticipatory component, sometimes referred to as the stimulus-preceding negativity (SPN), can be isolated from the CNV in tasks where a warning cue signals an impending stimulus to which no response is required, thereby eliminating response preparation processes (Brunia and van Boxtel, 2001).

The CNV preceding an imperative stimulus is typically followed by a positive voltage around 300 ms following the stimulus, leading to early debates about whether the P300 to the post-imperative stimulus in CNV-generating paradigms may simply reflect the resolution of the CNV (Donchin and Smith, 1970a,b). Subsequent studies provided evidence that the CNV and P300 reflect independent phenomena (Donchin and Heffley, 1979; Donchin et al., 1975; Hillyard et al., 1971), although the problems of differential CNV activity during the baseline periods preceding different task stimuli, and its confounding influence on the measurements of post-imperative stimulus ERP components, continue (Oddy et al., 2005).

Attempts to remove the influence of the CNV when assessing post-imperative stimulus ERP components have included choosing different baselines for different task conditions in order to avoid CNV activity (Oddy et al., 2005; Simson et al., 1977; Stadler et al., 2006), isolation and extraction of the CNV using PCA (Donchin et al., 1975; Oddy et al., 2005) and high pass filtering (Pollux and Guo, 2009). Of note, prior studies have found reduced amplitudes of the CNV (Klein et al., 1996), (Reuter et al., 2006; Rockstroh et al., 1994; van den Bosch, 1983; Verleger et al., 1999; Wagner et al., 1996) and the SPN (Reuter et al., 2006) in schizophrenia, indicating deficiencies in orienting, motor preparation and stimulus anticipation.

1.5. ERPs to unattended deviant events

As discussed above, a standard tone can acquire “deviance” status based on its unlikely position in a sequence. A series of ERP components might be elicited that are sensitive to non-target events during a cognitive task, including MMN, N2, and P3a. Naatanen et al. (1982) divided the N2 into MMN and N2b components, which can be distinguished on the basis of their dependence on attention and scalp topography. While MMN to a deviant auditory event can be elicited without attention being directed to the auditory stream, MMN is overlapped by the N2b when elicited during a cognitive task (Näätänen et al., 1993). While it is difficult to rule out attention from most paradigms, these two components can be distinguished by their scalp topographies; MMN reverses polarity below the Sylvian fissure and N2b does not. Important to this report are studies showing schizophrenia-related reductions of MMN (see Umbricht and Krljes, 2005 for a meta-analysis), N2 (e.g., Umbricht et al., 2006), and P3a, as cited above.

1.6. Behavioral indices of expectancy

Before P300 was used to index expectancy in 1976 (Squires et al., 1976), reaction times (RT) were used to measure sequential dependencies in choice reaction time tasks (Remington, 1969). The more expected the imperative stimulus, the faster the RT should be. Although RTs are consistently slower in patients with schizophrenia than in controls (Nuechterlein, 1977), motor responses are more distal from the activity of interest than are ERPs, and hence may be less sensitive to the subtle schizophrenia effects we are exploring in this paper.

1.7. Goals of this paper

In this paper, we focus on data collected in a 3-stimulus auditory oddball task for another purpose and published elsewhere (Ford et al., 2008; Mathalon et al., 2010a). In those papers, we focused on the P3b and P3a to target and novel events, respectively. In this paper, we focus on the responses associated with standard events, as a function of the expectancies generated by trial-to-trial probabilities.

We predicted that when a standard tone is improbable based implicitly on the preceding sequence of stimuli, its appearance would be surprising and would therefore elicit a P300. Although others (Donchin, 1981; Duncan-Johnson and Donchin, 1980; Johnson and Donchin, 1982; Squires et al., 1976) assessing sequential probability effects on P300 focused on the P3b component, our analysis focused on task irrelevant standards. We predicted P3a, rather than P3b, would be elicited, as an unexpected standard is likely to engage attention in a “bottom-up” manner similar to novel distractors. By similar reasoning, we predicted that an N2b/MMN would be elicited by unexpected events due to the “deviance” acquired by virtue of their position in the sequence. To the extent that a CNV/SPN would also reflect anticipation of a target or novel deviant stimulus, respectively, we predicted that healthy controls would generate a CNV/SPN late in a sequence of consecutive standards, reflecting their emerging expectation that it was “time for a change”, i.e., that a deviant stimulus was imminent. To the extent that RTs provide another measure of expectancy (Remington, 1969), we expected, RTs to the targets would be faster as the target became more likely.

Based on the hypothesis that patients with schizophrenia are particularly deficient in processing implicit contextual cues, we predicted that patients with schizophrenia would be less likely to form normal expectancies from the context created by the local stimulus sequence and thus, would be less surprised by a late appearing standard in a consecutive series of standards and less likely to consider a late appearing standard to be deviant. Therefore, we predicted that patients would show a markedly reduced or absent P3a and N2b/MMN to sequentially improbable but otherwise indistinguishable standard stimuli within the stimulus sequence of a typical 3-stimulus auditory oddball task. Again, assuming that patients are deficient in implicitly developing expectancies based on the local stimulus sequence, we predicted that patients, relative to controls, would show less evidence of this CNV/SPN. Finally, we predicted that RT would also be sensitive to group differences in expectancy.

2. Nomenclature

In the balance of this paper, we refer to the P300 elicited by target stimuli as “P3b”. We refer to the P300 elicited by novel distractor stimuli as “P3a”. With appropriate caveats, we refer to the late positive component elicited by an unexpected standard tone as “P3a”. In the aggregate, they may be referred to as “P300s”. Similarly, because of the possibility that the earlier negative component elicited by the unexpected standard is an amalgam of N2b and MMN, we will refer to it as N2b/MMN.

3. Methods

3.1. Participants

Electroencephalography (EEG) data were acquired from patients with schizophrenia (SZ; $n = 21$), and healthy control subjects (HC; $n = 22$). All gave written informed consent after procedures had been fully described. Institutional Review Boards at the West Haven VA and Yale University approved this study.

Patients were recruited from community mental health centers and outpatient services of the VA Connecticut Healthcare System. Also, some patients were recruited by Dr. Hoffman to participate in a

repetitive transcranial magnetic stimulation (rTMS) clinical trial for auditory hallucinations, in which case they were studied before initiating rTMS treatment. All met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia based on a Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Patients with DSM-IV alcohol or drug abuse in the 30 days preceding the study were excluded. Patients were not excluded for past dependence on alcohol or drugs. Patients with schizoaffective disorder were excluded. Symptoms were rated using the Positive and Negative Symptom Scale (Kay et al., 1987).

Healthy control subjects were recruited by newspaper advertisements and word-of-mouth, screened by telephone using questions from the SCID (First et al., 1995) non-patient screening module, and excluded for any history of Axis I psychiatric illness. All participants were excluded for significant head injury (prolonged loss of consciousness), neurological disorders, or medical illnesses compromising the central nervous system.

ERP data from 5 patients were excluded due to low trial numbers (<10) in one or more conditions of interest. Demographic and clinical data for the remaining subjects in both groups are summarized in Table 1.

3.2. Task

In the 3-stimulus auditory oddball task, a pseudorandom series of frequent (70%) “standard” low tones (500 Hz), infrequent (15%) “target” high tones (1000 Hz), and infrequent novel distractor sounds (15%), were presented with a 1.25 second stimulus onset asynchrony. Novel sounds were selected from a corpus of sounds developed by Friedman (Friedman et al., 1993). The tones were 50 ms in duration and 80 dB SPL (C scale). Novel sounds ranged between 175 and 250 ms in duration and averaged 80 dB SPL (C scale).

A total of 300 auditory stimuli were presented: 210 standards, 45 targets and 45 novel distractors, thus the global probability of a deviant (D) was 0.3 and the global probability of a standard (S) was 0.7. The sequence was constrained so that there was always one

standard following a deviant. Because the sequence was not random, the actual sequential probability of a standard is not the same as the mathematically calculated conditional probability. That is, the probability of two standards occurring in a row is not 0.7×0.7 , and likewise, the probability of three standards in a row is not $0.7 \times 0.7 \times 0.7$.

In Table 2, we show two possible approaches to describing the sequential probabilities of standards subsequent to the appearance of a deviant (target or novel) in our stimulus sequence. In the first approach, we calculate the conditional probabilities of 1, 2, 3, or 4 consecutive standards, given that a deviant has occurred. For example, the probability of three consecutive standards (S–S–S) following a deviant (D) is 0.40, and the probability of 4 consecutive standards (S–S–S–S) following a deviant is 0.16. In the second approach, we calculate the probability that a standard will appear, given that a deviant plus 0, 1, 2, or 3 standards has occurred. For example, the probability of a third standard given a prior sequence of D–S–S is 0.56, and the probability of a fourth standard given a prior sequence of D–S–S–S is 0.40. Regardless of the approach, the 4th standard in a row is less probable than the 2nd or 3rd standard in a row. It is important to note that our oddball stimulus sequence never contained 5 consecutive standards and never contained 6 or more consecutive standards.

3.3. Measures

Subjects sat in an acoustically shielded booth in front a computer monitor and wore headphones. EEG was recorded at 1000 Hz from 26 scalp sites, bandpass-filtered between 0.05 and 100 Hz, and referenced to linked ears. Additional electrodes were placed at the outer canthi of both eyes and above and below the left eye to record eye movements and blinks (vertical and horizontal electro-oculogram [EOG]; VEOG, HEOG). All electrode impedances were maintained at or below 10 k Ω , with most EEG sites near 5 k Ω .

Except for topographic scalp maps, which are based on the entire electrode montage, the analyses for P3a are based on F3, Fz, F4, C3, Cz, C4, P3, Pz and P4, analyses for N2b/MMN are based on Fz and Cz, and analyses for CNV/SPN are based on C3, Cz, C4, P3, Pz, and P4.

Table 1
Demographics of populations studied.

| Variable | Healthy control (HC) subjects <i>n</i> = 22 | | | | Schizophrenic (SZ) patients <i>n</i> = 16 | | | |
|---|---|-------|------|------|---|-------|-------|-------|
| | Mean | SD | Min | Max | Mean | SD | Min | Max |
| Age (years) <i>p</i> = 0.62 | 37.29 | 12.62 | 23 | 59 | 39.27 | 11.26 | 22.00 | 56.12 |
| Education (years) <i>p</i> < 0.0007; HC > SZ | 16.23 | 2.28 | 12.0 | 20.0 | 13.75 | 1.61 | 12.00 | 16.00 |
| Average parental socioeconomic status* <i>p</i> = 0.78 | 34.61 | 15.16 | 11.0 | 62.0 | 36.13 | 17.14 | 11.00 | 68.00 |
| Mean symptom scores** | | | | | | | | |
| Positive PANSS | | | | | 17.54 | 4.82 | 12.00 | 25.00 |
| Negative PANSS | | | | | 15.64 | 5.04 | 9.00 | 22.00 |
| General PANSS | | | | | 33.39 | 9.34 | 20.00 | 54.00 |
| Anxiety | | | | | 2.72 | 1.36 | 1.00 | 5.00 |
| Depression | | | | | 2.86 | 1.29 | 1.00 | 5.00 |
| Hallucinations | | | | | 4.00 | 2.08 | 1.00 | 6.00 |
| Delusions | | | | | 3.07 | 1.54 | 1.00 | 6.00 |
| Handedness | 19 right, 2 left, 1 ambidextrous | | | | 15 right, 1 left | | | |
| Gender | 9 women, 13 men | | | | 3 women, 13 men | | | |
| Diagnosis | | | | | 2 Undifferentiated Schizophrenia 14 Paranoid Schizophrenia | | | |
| Age at illness onset* | | | | | 21.07 | 3.28 | 17.00 | 28.00 |
| Duration illness* | | | | | 17.90 | 11.06 | 9.200 | 36.12 |
| Antipsychotic type | | | | | 11 atypical, 1 typical, 4 both | | | |

* Missing data for 1 SZ.

** Missing data for 2 SZ.

Table 2

| Stimulus sequence (ERP elicited by last standard, S) | Number of trials | Conditional probability structure | Conditional probability |
|--|------------------|-----------------------------------|-------------------------|
| <i>Conditional probability of consecutive standards, given a deviant stimulus</i> | | | |
| DS | 90 | Probability (S D) | 1.00 |
| DSS | 62 | Probability (SS D) | 0.71 (62/87*) |
| DSSS | 35 | Probability (SSS D) | 0.40 (35/87) |
| DSSSS | 14 | Probability (SSSS D) | 0.16 (14/87) |
| <i>Conditional probability of last standard, given prior deviant-standard sequence</i> | | | |
| DS | 90 | Probability (S D) | 1.00 |
| DSS | 62 | Probability (S DS) | 0.71 (62/87) |
| DSSS | 35 | Probability (S DSS) | 0.56 (35/62) |
| DSSSS | 14 | Probability (S DSSS) | 0.40 (14/35) |

* There were 90 deviants, each of which was followed by at least one standard. Each of the 3 runs ended with a deviant followed by only a single standard. The other 87 deviants were followed by at least 2 standards.

ERP data processing involved the following steps. Continuous EEG data were low pass-filtered at 12 Hz before being separated into epochs. In order to minimize the influence of differential CNV/SPN activity during the pre-stimulus baseline on the measurements of P3a and N2b/MMN, an additional 1 Hz high pass filter was applied to the continuous EEG data before parsing them into epochs for P3a and N2b/MMN assessment, but not before parsing the data into epochs for CNV/SPN assessment.

To assess CNV/SPN activity subsequent to a standard in anticipation of the next stimulus, continuous EEG data were parsed into 1350 ms epochs beginning 100 ms prior to each standard and ending at the onset of the next stimulus (irrespective of whether it was a standard or a deviant). Epochs were binned and averaged separately for Standard #1 ($n = 87$ trials), Standard #2 ($n = 62$ trials), and Standard #3 ($n = 35$ trials). The last 50 ms of each of these ERP epochs was interrogated in order to assess whether a CNV/SPN preceded the subsequent stimulus.

To assess P3a and N2b/MMN elicited by standards, we generated 1000 ms EEG epochs time-locked to the onset of each standard with a 100 ms pre-stimulus baseline. Standard EEG epochs were then binned according to the number of intervening standards between the eliciting standard and the preceding deviant (irrespective of whether it was a target or a novel stimulus): Standard #1 = first standard after a deviant, DS ($n = 90$ trials), Standard #2 = second consecutive standard after a deviant, DSS ($n = 62$ trials), Standard #3 = third consecutive standard after a deviant, DSSS ($n = 35$ trials), and Standard #4 = fourth consecutive standard after a deviant, DSSSS ($n = 14$ trials).

Based on the assumption that the ERP to Standard #1 had both an N1 and P2, but negligible N2b/MMN or P3a activity, we subtracted the ERP to Standard #1 from the ERPs to Standards #2, #3, and #4 to extract the N2b/MMN from the N1, and P3a from the P2. All analyses of P3a and N2b/MMN are based on values extracted from these difference waveforms.

VEOG and HEOG data were used to correct the EEG epochs for eye movements and blinks with a regression-based algorithm (Gratton et al., 1983). Epochs were then baseline corrected using the 100 ms pre-stimulus baseline, and epochs containing artifacts (voltages exceeding $\pm 100 \mu\text{V}$) were rejected. Standard trials associated with false alarm responses were rejected. Subjects with fewer than 10 trials remaining to Standard #4 were dropped from the analysis and are not represented in Table 1.

Fig. 1 shows the grand average ERPs for four consecutive standards following a deviant stimulus with and without application of the 1 Hz high pass filter. As can be seen in the healthy control waveforms that were not subjected to the 1 Hz filter, a CNV/SPN was evident prior to Standard #4, and a relatively large P3a was evident after it. Fig. 1 also

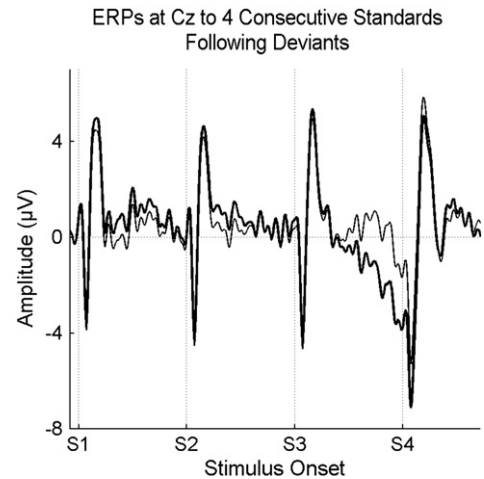


Fig. 1. Grand average ERPs for 4 consecutive standards following a deviant stimulus in healthy controls for Cz. ERPs are time-locked to the first of the four consecutive standards. Time (seconds) is indicated on the x-axis and amplitude (microvolts) on the y-axis. Positivity relative to the reference electrodes is plotted up. Vertical lines show the onsets of each Standard in the 4-standard sequence. Note that only Standard #4 evokes a P3a and is preceded by a CNV/SPN. Dotted lines show waveforms based on 1 Hz high pass-filtered continuous data, illustrating how this high pass filter effectively removes the CNV/SPN prior to Standard #4 while leaving the P3a following this standard largely intact.

shows that the 1 Hz high pass filter effectively removed the CNV/SPN preceding Standard #4 and modestly attenuated the P3a.

The upper portion of Fig. 2 shows the grand average ERPs to Standards #1, #2, #3, and #4 overlaid, rather than consecutively, as seen in Fig. 1. As can be seen in this illustration, P3a was not as evident in association with Standard #1, #2, or #3 as with Standard #4, and appeared to be attenuated in the schizophrenia patients. The lower portion of Fig. 2 shows the difference waveforms resulting from the subtraction of Standard #1 from the ERPs to the other standards. P3a and N2b/MMN can be seen to the Standard #4 difference waveform without contamination from P2 and N1, respectively.

Fig. 3 allows the comparison of the ERPs to Target and Novel stimuli and to Standard #4 (after subtraction of the ERP to Standard #1). The P3b to the targets and the P3a to the novel stimuli are denoted by arrows in Fig. 3. The topographic maps are scaled separately for each stimulus type to illustrate the similar scalp topography of the P3a to Standard #4 and the P3a to the novel distractor, supporting our suggestion that Standard #4 elicits a P3a rather than a P3b. Also apparent in Fig. 3 is the N2b/MMN to Standard #4, as denoted by an arrow.

Fig. 4 displays the scalp topography of the N2b/MMN extracted from the difference waveforms. As can be seen in this illustration, N2b/MMN was less evident in association with Standards #2 and #3, than Standard #4, and is attenuated in the schizophrenia patients. In both groups, N2b/MMN has the expected frontal central midline distribution.

3.4. ERP component identification and measurement

From the difference waveforms for Standards #2, #3, and #4, P3a was quantified at each electrode as the mean voltage across a 275 to 400 ms time-window, relative to stimulus onset. Also from the difference waveforms, the N2b/MMN peak was identified between 90 and 225 ms at Fz. This latency ± 25 ms was the search window for N2b/MMN at other sites. N2b/MMN was quantified as the area ± 25 ms around the peak.

To assess the amplitude of the CNV/SPN following Standard #3 and preceding the next stimulus "X" (which could be a deviant or a standard), the mean voltage values from the central (C3, Cz and C4) and parietal (P3, Pz and P4) electrode rows were extracted for 1201–1250 ms, corresponding to the -50 to 0 ms preceding stimulus X in

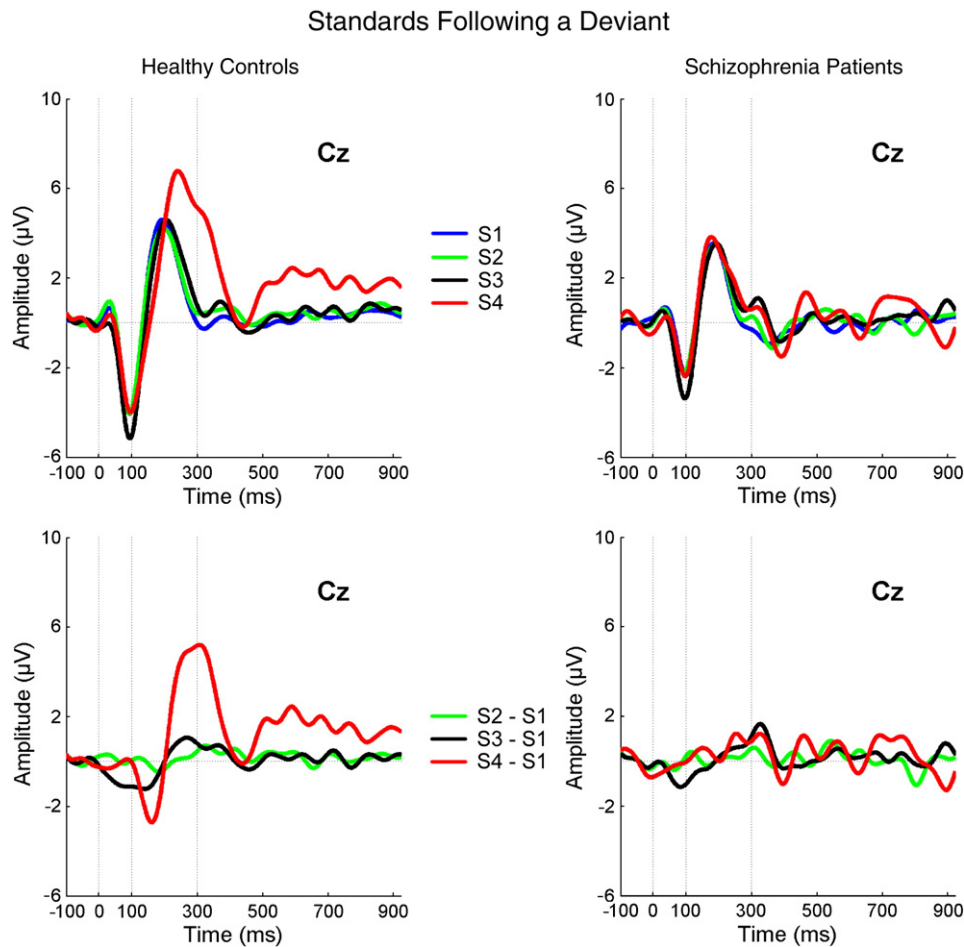


Fig. 2. (Top) Grand average ERPs based on 1 Hz high pass-filtered data are superimposed for Standards #1, #2, #3, and #4, each corrected by the 100 ms pre-stimulus baseline, in healthy controls (left) and patients with schizophrenia (right) at Cz. Time is shown on the x-axis, and voltage on the y-axis. Positivity relative to the reference electrodes is plotted up. (Bottom) Grand average ERPs resulting from the subtraction of the ERP to Standard #1 from each of the other Standards (S2 – S1, S3 – S1, and S4 – S1). Data extracted from these difference waveforms were statistically analyzed.

the sequence DSSS–X. Mean voltage values were similarly extracted with respect to Standard #2 (i.e., DSS–X) and Standard #1 (i.e., DS–X). The CNV/SPN topographic maps representing this activity are shown for each group in Fig. 4.

3.5. Statistical analysis

P3a area was analyzed in a 4-way repeated measures analysis of variance (ANOVA) with Group (healthy controls vs. schizophrenia patients) as a between-subjects factor, and within-subjects factors of Standard Number (#2, #3 or #4), Anterior–posterior (A–P) region (frontal, central and parietal) and Lateral region (left, midline and right).

N2b/MMN area was analyzed in a 3-way ANOVA with Group as a between-subjects factor, and within-subjects factors of Standard Number (#2, #3, or #4) and a midline A–P factor (Fz and Cz).

For P3a and N2b/MMN, Group \times Standard Number interactions were followed-up by testing the Standard Number effect in each group separately, followed by Helmert contrasts (#2 vs. #3, mean of #2 and #3 vs. #4). In addition, Groups were compared for each consecutive standard.

CNV/SPN amplitude measured at central and parietal sites was analyzed in a 4-way ANOVA model with Group as a between-subjects factor, and within-subjects factors of A–P region (central and parietal), Lateral region (left, midline and right), Sequence preceding X (DS–X, DSS–X and DSSS–X). Follow-up tests were similar to those for P3a and N2b/MMN.

Median RTs were analyzed in a 2-way ANOVA for the between-subjects factor of Group and the within-subjects factor of Sequence preceding a target (DS–T, DSS–T, DSSS–T, and DSSSS–T).

4. Results

The results of the main ANOVA, contrasts, and follow-up tests appear in Tables 3, 4, and 5 for P3a, N2b/MMN and CNV. Only significant findings involving Group and Number will be discussed. These appear in bold font in the tables.

4.1. P3a amplitude

P3a to Standard #4 peaked earlier in controls (318 ms) than in patients (367 ms), $F(1,36) = 5.21, p = 0.028$.

There were significant main effects of Group and Standard Number, as well as a significant Group \times Standard Number interaction for P3a to the Standards. This interaction was parsed by conducting separate Standard Number \times A–P region \times Laterality region ANOVAs within each group. Although the effect of Standard Number was larger in the controls than patients, the effect was significant in both groups. Follow-up Helmert contrasts indicated that, in both groups, P3a to Standards #2 and #3 did not differ from each other, but that P3a to Standard #4 differed from the average of P3a to Standards #2 and #3. Furthermore, this effect was greater in the controls than patients. Finally, P3a to each standard was assessed for the effect of Group; controls had a significantly larger P3a to Standard #4 than did

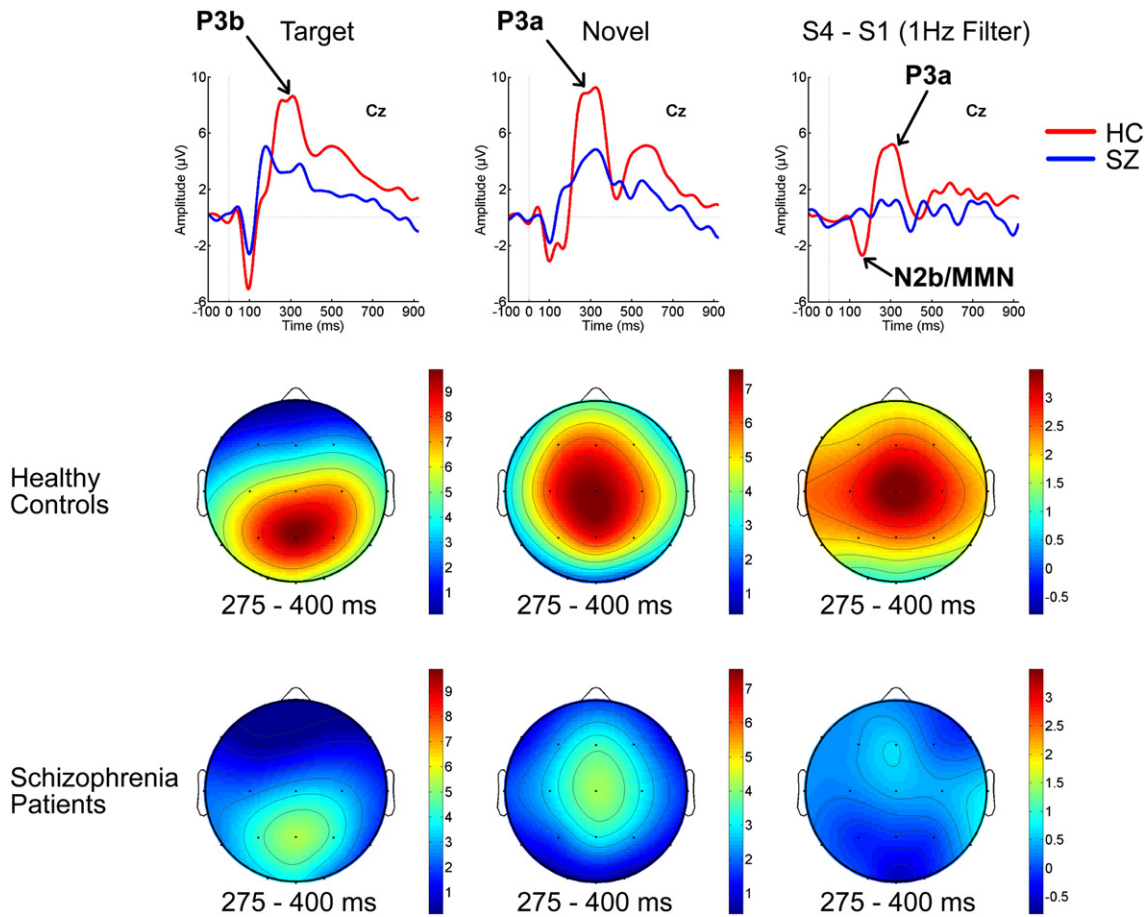


Fig. 3. (Top) Grand average ERPs (top section) for Targets, Novels, and the fourth consecutive standard (Standard #4 – Standard #1; S4 – S1) in healthy controls (HC), schizophrenia patients (SZ) are plotted from electrode Cz. Time is shown on the *x*-axis, and voltage on the *y*-axis. Positivity relative to the reference electrodes is plotted up. Note that the P3a elicited by Standard #4 and the P3a elicited by the Novel have similar latencies and morphologies. The ERP to Standard #4 is filtered with a 1 Hz high-pass filter; ERPs to the Target and Novel are not. (Bottom) Scalp topography voltage maps for Targets, Novels, and Standard #4 – Standard #1 are shown for the positive peak chosen individually for each subject and each stimulus (see text for description of peak picking algorithm). Voltage is scaled separately for each stimulus type in order to illustrate the similar topographies of the P3a to Standard #4 and to the novel distractors.

patients. No Group effects were seen for Standard #2 or #3. We also measured the peak of the P3a to Standard #4 and found that it too was reduced in patients compared to controls ($F(1,36) = 7.42, p = 0.01$).

4.2. N2b/MMN amplitude

N2b/MMN to Standard #4 peaked at 159 ms in both groups.

As can be seen in Table 4, there was a significant main effect of Standard Number and a Group \times Standard Number interaction. This interaction was parsed as above, using the same type of contrasts. In controls, there was a significant effect of Standard Number, with follow-up Helmert contrasts indicating that N2b/MMN to Standard #3 was larger than to Standard #2, and N2b/MMN to Standard #4 was larger than the mean of the others. These effects were not seen in the patients. Finally, N2b/MMN to each standard was assessed for the effect of Group; controls had a significantly larger N2b/MMN to Standard #4 than did patients. No Group effects were seen for Standard #2 or #3 (20 ms).

4.3. CNV/SPN

As can be seen in Table 5, there were significant main effects of Group and Standard Number, as well as a significant Group \times Standard Number interaction for CNV/SPN. The interaction was parsed as

described above for P3a, using the same type of contrasts. In controls, there was a significant Standard Number effect, with follow-up Helmert contrasts indicating that the CNV/SPN developing after Standards #1 and #2 did not differ, but that the CNV/SPN developing after Standard #3 did differ from the average of Standards #1 and #2. In contrast, the Standard Number effect was not significant in patients.

To further parse the Group \times Standard Number interaction, the groups were compared for the CNV/SPN developing after Standard #3 and the average of the response developing after Standards #1 and #2. Healthy controls developed a significantly larger response following Standard #3 and then following the previous Standards.

4.4. Relationships among ERP measures

Given that the ERP measures elicited by, or proceeding, Standard #4 might provide somewhat redundant information, we assessed their inter-correlations in each group for CNV/SPN, P3a and N2b/MMN at Cz. CNV/SPN and P3a were correlated in healthy controls ($r = -0.55, p = 0.008$) and patients ($r = -0.51, p = 0.046$). N2b/MMN and P3a were correlated in healthy controls ($r = -0.52, p = 0.01$), but not in patients ($r = 0.42, p = 0.11$).

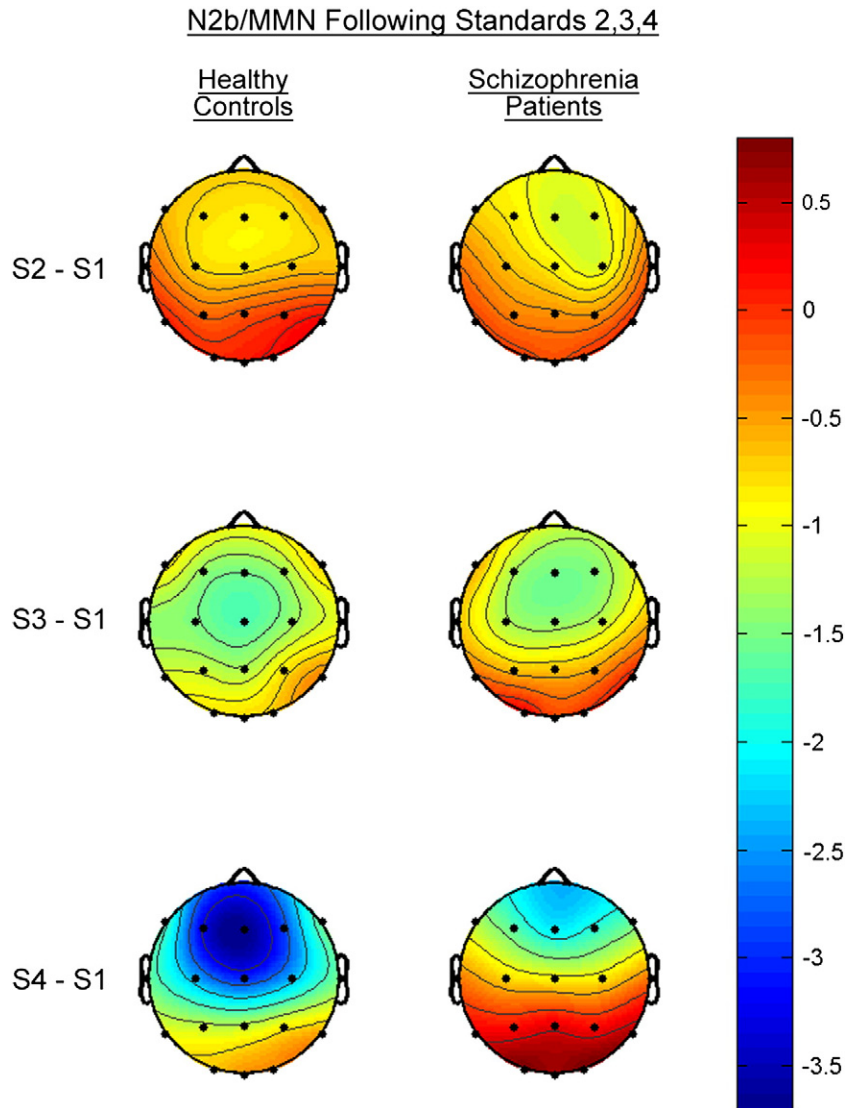


Fig. 4. Topographic voltage maps showing average voltages for 50 ms around the peak of the N2b/MMN derived by subtracting the ERP to Standard #1 from the ERPs to each of the other Standards (S2 – S1, S3 – S1, and S4 – S1).

4.5. Median RT

Reaction times provide another measure of expectancy (Remington, 1969). As expected, RTs to the target decreased as the target became more likely ($F(3,108) = 19.80, p < 0.0001$). This effect did not differ in patients and controls ($F(3,108) = 0.37, p = 0.72$). Patients (391 ms) responded more slowly than the controls (323 ms), $F(1,360) = 11.77, p = 0.002$.

5. Discussion

To the extent that a subject is aware of the context set up by local probabilities, an expectation may be established for one event or another. A violation of this expectancy will elicit a P300 (Duncan-Johnson and Donchin, 1977; Squires et al., 1976). Although the global probability of a standard tone was $p = 0.70$ in our paradigm, the sequential probability of a standard varied from $p = 1.0$ to 0.16. The low probability standard was preceded by a CNV/SPN and elicited an N2b/MMN and P3a in healthy control subjects, suggesting they developed the expectation that it was “time for a change.” When the change did not occur, their expectations were violated. Given the large N2b/MMN and P3a elicited by the fourth consecutive standard following a deviant stimulus, and the CNV/SPN that selectively

emerges following the third consecutive standard, we suggest that healthy controls are processing the sequential probabilities of standards by implicitly asking, “What’s the likelihood of seeing four standards in a row following a deviant stimulus?” The answer is, “Not very likely.” Thus, after 3 consecutive standards, subjects who implicitly processed the local stimulus context established by sequential probabilities began to expect that a deviant (target or novel) stimulus was imminent, generating a CNV/SPN, and furthermore, they were surprised by the appearance of a fourth consecutive standard, thereby generating a N2b/MMN and a P3a. Although their analyses differed from ours, others have reported similar effects to those observed in our study for P300 (Gilmore et al., 2005; Stadler et al., 2006).

It is critical to note that no other features of the standard tone that elicited an N2b/MMN or a P3a made it deviant or salient other than the violation of the expectancy that four standards in a row was unlikely. Thus, while the salience of targets was based on their pitch, task relevance, and probability, the salience of the fourth standard in a row was based only on the low probability of this pattern occurring. Similarly, the salience of novels was based on both low probability and their ever-changing content.

Patients with schizophrenia did not generate a P3a to the fourth standard in a row. This could result from at least two abnormalities:

Table 3
ANOVA for P3a area to Standards #2, #3, and #4*.

| Group effects | df | F | Sig. |
|--|-------|--------------|---------------|
| Group (HC vs. SZ) | 1,36 | 6.12 | 0.02 |
| Number (2nd, 3rd, 4th Standards) | 2,72 | 19.93 | 0.0001 |
| Group x Number | 2,72 | 6.06 | 0.01 |
| Effect of number in each group | | | |
| Effect of number for controls | 2,42 | 19.24 | 0.0001 |
| Effect of number for patients | 2,30 | 5.73 | 0.009 |
| Number contrasts within controls | | | |
| Standard#3 vs. Standard#2 | 1,21 | 0.82 | 0.38 |
| Standard#4 vs. Previous (#2, #3) | 1,21 | 20.56 | 0.0001 |
| Number contrasts within patients | | | |
| Standard#3 vs. Standard#2 | 1,15 | 2.18 | 0.16 |
| Standard#4 vs. Previous (#2, #3) | 1,15 | 9.39 | 0.008 |
| Effect of group for each contrast | | | |
| Standard#3 vs. Standard#2 | 1,36 | 0.67 | 0.42 |
| Standard#4 vs. Previous (#2, #3) | 1,36 | 6.89 | 0.01 |
| Effect of group for each standard | | | |
| Group effects at Standard #2 | 1,36 | 0.32 | 0.58 |
| Group effects at Standard #3 | 1,36 | 0.08 | 0.78 |
| Group effects at Standard #4 | 1,36 | 9.04 | 0.005 |
| A–P (anterior–posterior: frontal vs. central vs. parietal) | 2,72 | 2.66 | 0.10 |
| A–P Group | 2,72 | 0.21 | 0.71 |
| Lateral (left vs. mid vs. right) | 2,72 | 23.51 | 0.0001 |
| Lateral Group | 2,72 | 1.49 | 0.23 |
| Number A–P | 4,144 | 1.91 | 0.15 |
| Number A–P Group | 4,144 | 0.15 | 0.87 |
| Number Lateral | 4,144 | 6.82 | 0.0001 |
| Number Lateral Group | 4,144 | 0.86 | 0.46 |
| A–P Lateral | 4,144 | 3.51 | 0.02 |
| A–P Lateral Group | 4,144 | 1.24 | 0.30 |
| Number A–P Lateral | 8,288 | 2.33 | 0.05 |
| Number A–P Lateral Group | 8,288 | 1.65 | 0.16 |

* Significant effects of interest are in bold font.

Patients may not orient to unexpected events, or they may be unable to learn from the context that an event is unexpected. In their seminal report, Roth and Cannon (Roth and Cannon, 1972) used an infrequent, unattended white noise to elicit a P300 (or P3a), and they related its elicitation to the orienting response, and hence its reduction in schizophrenia patients to an alteration in orienting. That the late positive component to the fourth standard in a row had the same

Table 4
ANOVA for N2b/MMN area to Standards #2, #3, and #4*.

| Group effects | Df | F | Sig. |
|--|------|--------------|---------------|
| Group (HC vs.SZ) | 1,36 | 1.423 | 0.24 |
| Number (2nd, 3rd, 4th Standards) | 2,72 | 8.321 | 0.001 |
| Group x Number | 2,72 | 4.852 | 0.01 |
| Effect of number in each group | | | |
| Effect of number for controls | 2,42 | 15.68 | 0.0001 |
| Effect of number for patients | 2,30 | 0.38 | 0.67 |
| Number contrasts within controls | | | |
| Standard#3 vs. Standard#2 | 1,21 | 4.206 | 0.05 |
| Standard#4 vs. Previous (#2, #3) | 1,21 | 20.14 | 0.0001 |
| Number contrasts within patients | | | |
| Standard#3 vs. Standard#2 | 1,15 | 0.494 | 0.49 |
| Standard#4 vs. Previous (#2, #3) | 1,15 | 0.223 | 0.64 |
| Effect of group for each contrast | | | |
| Standard#3 vs. Standard#2 | 1,36 | 0.181 | 0.67 |
| Standard#4 vs. Previous (#2, #3) | 1,36 | 8.112 | 0.007 |
| Effect of group for each standard | | | |
| Group effects at Standard #2 | 1,36 | 0.698 | 0.41 |
| Group effects at Standard #3 | 1,36 | 0.001 | 0.98 |
| Group effects at Standard #4 | 1,36 | 6.879 | 0.01 |
| A–P (anterior–posterior: frontal vs. central vs. parietal) | 2,72 | 0.378 | 0.54 |
| A–P Group | 2,72 | 0.534 | 0.47 |
| Number A–P | 2,72 | 7.85 | 0.002 |
| Number A–P Group | 2,72 | 0.252 | 0.72 |

* Significant effects of interest are in bold font.

Table 5
ANOVA for CNV/SPN following Standards #1, #2 and #3*.

| Group effects | df | F | Sig. |
|--|-------|--------------|-------------|
| Group (HC vs. SZ) | 1,36 | 15.13 | 0.00 |
| Number (CNV following Standard #1, #2 and #3) | 2,72 | 9.73 | 0.00 |
| Group x Number | 2,72 | 4.04 | 0.02 |
| Effect of number in each group | | | |
| Effect of number for controls | 2,42 | 17.46 | 0.00 |
| Effect of number for patients | 2,30 | 0.72 | 0.49 |
| Number contrasts within controls | | | |
| Standard#3 vs. Standard#2 | 1,21 | 1.62 | 0.22 |
| Standard#4 vs. Previous (#2, #3) | 1,21 | 27.23 | 0.00 |
| Effect of group for each contrast | | | |
| Standard#3 vs. Standard#2 | 1,36 | 1.40 | 0.24 |
| Standard#4 vs. Previous (#2, #3) | 1,36 | 6.13 | 0.02 |
| Effect of group for each standard | | | |
| Group effects before Standard #2 | 1,36 | 3.78 | 0.06 |
| Group effects before Standard #3 | 1,36 | 0.05 | 0.83 |
| Group effects before Standard #4 | 1,36 | 11.93 | 0.00 |
| A–P (anterior–posterior: frontal vs. central vs. parietal) | 1,36 | 5.06 | 0.03 |
| A–P Group | 1,36 | 6.93 | 0.01 |
| Lateral (left vs. mid vs. right) | 2,72 | 7.44 | 0.00 |
| Lateral Group | 2,72 | 2.09 | 0.14 |
| Number A–P | 2,72 | 24.61 | 0.00 |
| Number A–P Group | 2,72 | 1.06 | 0.35 |
| Number Lateral | 4,144 | 8.87 | 0.00 |
| Number Lateral Group | 4,144 | 1.40 | 0.25 |
| A–P Lateral | 4,144 | 5.09 | 0.01 |
| A–P Lateral Group | 4,144 | 2.47 | 0.09 |
| Number A–P Lateral | 4,144 | 3.66 | 0.01 |
| Number A–P Lateral Group | 4,144 | 1.39 | 0.24 |

* Significant effects of interest are in bold font.

scalp distribution as the P3a to a novel sound supports the contribution of orienting to the positivity elicited by Standard #4. However, arguing against a failure of the orienting response in schizophrenia are reports of normal P300s in patients to isolated targets (Roth et al., 1991; Shelley et al., 1996) and startling noises (Ford et al., 1999) that occur at very long inter-target intervals with no intervening standards, a situation likely to elicit orienting. Instead, we suggest that patients with schizophrenia fail to use context to form expectations about pattern violations.

Our conclusion that these ERP abnormalities in patients result from a failure to use context is consistent with behavioral (Barch et al., 2001; Carter et al., 2001; Ford et al., 2004a; Henik et al., 2002; Servan-Schreiber et al., 1996; Shelley et al., 1996) and P300 data (Shelley et al., 1996) collected during a working memory task (the AX-Continuous Performance Task, or AX-CPT). The same conclusion has been drawn from behavioral data collected during a Go–No Go task, showing that patients do not establish pre-potent responses supported by the context (Ford et al., 2004b).

Roth and Cannon discussed whether auditory neural recovery effects contributed to the P300 they reported. Their frequent event was a pure tone and their infrequent event was a white noise; and it could be argued that the white noise should stimulate new, fresh regions of auditory cortex, not already fatigued by processing the pure tone. This alone might produce a larger neural response. In the analysis we presented here, possible contributions of neural recovery effects to the P3a are obviated, as Standard #4 was immediately preceded by three other tones of the same pitch.

Our analysis provides a relatively pure assessment of expectancy and points to P3a as a sensitive index of the failure in schizophrenia patients to perceive context implicitly generated by local sequential probabilities. We therefore speculate that prior studies showing P300 amplitude reductions in schizophrenia may be related to an inability of schizophrenia patients to appreciate the context of the eliciting event, and not to failures of attention and orienting, or to differential effects of neural recovery.

The CNV/SPN prior to the fourth consecutive standard in healthy controls provided further evidence that they began to anticipate that it was time for a change, i.e., that a deviant stimulus was imminent. To diminish the impact of the CNV/SPN on the baseline prior to the standard that elicited a P3a, we high pass-filtered the data at 1 Hz to remove the CNV/SPN baseline negativity, and we still found the P3a effect.

As described in the Introduction, N2b often overlaps with MMN when attention is directed toward the auditory stream, as was this case in our oddball paradigm. N2b and MMN can be distinguished by their scalp topographies, with MMN reversing polarity over the Sylvian fissure when the data are referenced to activity recorded from the nose (Alho et al., 1986). Accordingly, we nose-referenced the ERP data recorded from electrodes below the Sylvian fissure (TP7 and TP8). While we did not subject these data to statistical analysis, we did note a slight polarity reversal suggesting contributions from a MMN in controls, but not in the patients. Regardless of its identity, the N2b/MMN was reduced in patients, consistent with reports in the literature for both MMN (Umbricht and Krljes, 2005) and N2b when extracted from difference waveforms (Kasai et al., 1999).

Reaction times also reflect expectations; however, unlike the CNV/SPN preceding Standard #4, and the N2b/MMN and P3a elicited by Standard #4, the RT data suggested that patients formed normal expectancies. If we had not recorded EEG, we would surmise from this analysis that patients and controls form expectancies in the same way. However, the ERP data suggest that more direct neural reflections of expectancy and expectancy violations in connection with the appearance of a fourth consecutive standard are abnormal in schizophrenia.

Finally, it is worth noting that although we refer to the positivity to Standard #4 as being a “P3a”, others might not. Indeed, Picton and Hillyard (1974) might have labeled it a “P250,” which they claim reflects automatic attentional mechanisms and stimulus classification. Laurent et al. (1999) suggested that P200 responses to non-targets might reflect how the brain processes information that is not task-relevant in an oddball paradigm, or, we would add, that becomes unexpected by its position in a series. Because it has a similar scalp distribution to the novelty P3a, we believe that the positivity elicited by Standard #4 is most likely a P3a.

One of the limitations of the current study is that the sequence of stimuli was not explicitly structured to allow a comparison with Duncan-Johnson et al. (1984). Their report was based on the analysis of ERPs to task-relevant (target) stimuli, presented in an equiprobable, random sequence. Our results are based on the analysis of ERPs to non-target standards, in a non-random sequence. Thus, we cannot directly compare their data to ours. Another limitation is that our conclusions are limited to patients treated with antipsychotic medications.

Acknowledgments

We thank Kevin Spencer for suggesting that Standard #4 might have elicited a MMN.

This work was supported by the VA Schizophrenia Biological Research Center (JMF), Research Career Scientist (JMF), VA Merit Review (JMF), NIMH (JMF, DHM, REH), NARSAD (JMF, DHM, REH), VA Career Award (DHM).

References

- Alho, K., Paavilainen, P., Reinikainen, K., Sams, M., Naatanen, R., 1986. Separability of different negative components of the event-related potential associated with auditory stimulus processing. *Psychophysiology* 23, 613–623.
- American Psychiatric Association, 1994. *Diagnostic and Statistical Manual of Mental Disorder (DSM-IV)*. American Psychiatric Association, Washington.
- Barch, D.M., Carter, C.S., Braver, T.S., Sabb, F.W., MacDonald III, A., Noll, D.C., Cohen, J.D., 2001. Selective deficits in prefrontal cortex function in medication-naïve patients with schizophrenia. *Archives of General Psychiatry* 58, 280–288.
- Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R.M., Frangou, S., 2004. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research* 70, 315–329.
- Brunia, C.H., van Boxtel, G.J., 2001. Wait and see. *International Journal of Psychophysiology* 43, 59–75.
- Carter, C.S., MacDonald III, A.W., Ross, L.L., Stenger, V.A., 2001. Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. *American Journal of Psychiatry* 158, 1423–1428.
- Donchin, E., 1981. Surprise! ... Surprise? *Psychophysiology* 18, 493–513.
- Donchin, E., Coles, M., 1988. Is the P300 component a manifestation of context updating? (Commentary on Verleger's critique of the context updating model). *Behavioral and Brain Sciences* 11, 357–374.
- Donchin, E., Heffley, E.F., 1979. The independence of the P300 and the CNV reviewed: a reply to Wastell. *Biological Psychology* 9, 177–188.
- Donchin, E., Smith, D.B., 1970a. The contingent negative variation and the late positive wave of the average evoked potential. *Electroencephalography and Clinical Neurophysiology* 29, 201–203.
- Donchin, E., Smith, D.D., 1970b. The CNV and the “late positive wave”—two sides of the same coin. *Electroencephalography and Clinical Neurophysiology* 28, 91–92.
- Donchin, E., Tueting, P., Ritter, W., Kutas, M., Heffley, E., 1975. On the independence of the CNV and the P300 components of the human averaged evoked potential. *Electroencephalography and Clinical Neurophysiology* 38, 449–461.
- Duncan-Johnson, C., Donchin, E., 1980. The relation of P300 latency to reaction time as a function of expectancy. *Progress in Brain Research* 54, 717–722.
- Duncan-Johnson, C.C., Donchin, E., 1977. On quantifying surprise: the variation in event-related potentials with subjective probability. *Psychophysiology* 14, 456–467.
- Duncan-Johnson, C.C., Roth, W.T., Kopell, B.S., 1984. Effects of stimulus sequence on P300 and reaction time in schizophrenics: a preliminary report. *Annals of New York Academy of Science* 425, 570–571.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Biometrics Research Department, New York State Psychiatric Institute, New York, NY.
- Ford, J.M., 1999. Schizophrenia: the broken P300 and beyond. *Psychophysiology* 36, 667–682.
- Ford, J.M., Gray, M., Whitfield, S.L., Turken, A.U., Glover, G., Faustman, W.O., Mathalon, D.H., 2004a. Acquiring and inhibiting prepotent responses in schizophrenia: event-related brain potentials and functional magnetic resonance imaging. *Archives of General Psychiatry* 61, 119–129.
- Ford, J.M., Gray, M., Whitfield, S.L., Turken, A.U., Glover, G., Faustman, W.O., Mathalon, D.H., 2004b. Acquiring and inhibiting prepotent responses in schizophrenia: event-related brain potentials and functional magnetic resonance imaging. *Archives of General Psychiatry* 61, 119–129.
- Ford, J.M., Roach, B.J., Hoffman, R.S., Mathalon, D.H., 2008. The dependence of P300 amplitude on gamma synchrony breaks down in schizophrenia. *Brain Research* 1235, 133–142.
- Ford, J.M., Roth, W.T., Menon, V., Pfefferbaum, A., 1999. Failures of automatic and strategic processing in schizophrenia: comparisons of event-related potential and startle blink modification. *Schizophrenia Research* 37, 149–163.
- Friedman, D., Simpson, G., Hamberger, M., 1993. Age-related changes in scalp topography to novel and target stimuli. *Psychophysiology* 30, 383–396.
- Gilmore, C.S., Clementz, B.A., Buckley, P.F., 2005. Stimulus sequence affects schizophrenia-normal differences in event processing during an auditory oddball task. *Brain Research. Cognitive Brain Research* 24, 215–227.
- Gonsalvez, C.L., Polich, J., 2002. P300 amplitude is determined by target-to-target interval. *Psychophysiology* 39, 388–396.
- Gonsalvez, C.J., Gordon, E., Anderson, J., Pettigrew, G., Barry, R.J., Rennie, C., Meares, R., 1995. Numbers of preceding nontargets differentially affect responses to targets in normal volunteers and patients with schizophrenia: a study of event-related potentials. *Psychiatry Research* 58, 69–75.
- Gratton, G., Coles, M.G.H., Donchin, E., 1983. A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology* 55, 468–484.
- Henik, A., Carter, C.S., Salo, R., Chaderjian, M., Kraft, L., Nordahl, T.E., Robertson, L.C., 2002. Attentional control and word inhibition in schizophrenia. *Psychiatry Research* 110, 137–149.
- Hillyard, S.A., Squires, K.C., Bauer, J.W., Lindsay, P.H., 1971. Evoked potential correlates of auditory signal detection. *Science* 172, 1357–1360.
- Jeon, Y.W., Polich, J., 2003. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology* 40, 684–701.
- Johnson Jr., R., 1986. A triarchic model of P300 amplitude. *Psychophysiology* 23, 367–384.
- Johnson Jr., R., Donchin, E., 1982. Sequential expectancies and decision making in a changing environment: an electrophysiological approach. *Psychophysiology* 19, 183–200.
- Kasai, K., Okazawa, K., Nakagome, K., Hiramatsu, K., Hata, A., Fukuda, M., Honda, M., Miyauchi, M., Matsushita, M., 1999. Mismatch negativity and N2b attenuation as an indicator for dysfunction of the preattentive and controlled processing for deviance detection in schizophrenia: a topographic event-related potential study. *Schizophrenia Research* 35, 141–156.
- Katayama, J., Polich, J., 1998. Stimulus context determines P3a and P3b. *Psychophysiology* 35, 23–33.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13, 261–276.
- Klein, C., Rockstroh, B., Cohen, R., Berg, P., 1996. Contingent negative variation (CNV) and determinants of the post-imperative negative variation (PINV) in schizophrenic patients and healthy controls. *Schizophrenia Research* 21, 97–110.
- Laurent, A., Garcia-Larrea, L., d'Amato, T., Bosson, J., Saoud, M., Marie-Cardine, M., Maugiere, F., Dalery, J., 1999. Auditory event-related potentials and clinical scores in unmedicated schizophrenic patients. *Psychiatry Research* 86, 229–238.

- Loveless, N.E., Sanford, A.J., 1974. Slow potential correlates of preparatory set. *Biological Psychology* 1, 303–314.
- Mathalon, D.H., Faustman, W.O., Ford, J.M., 2002. N400 and automatic semantic processing abnormalities in patients with schizophrenia. *Archives of General Psychiatry* 59, 641–648.
- Mathalon, D.H., Ford, J.M., Pfefferbaum, A., 2000. Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. *Biological Psychiatry* 47, 434–449.
- Mathalon, D.H., Hoffman, R.E., Watson, T.D., Miller, R.M., Roach, B.J., Ford, J.M., 2010a. Neurophysiological distinction between schizophrenia and schizoaffective disorder. *Frontiers in Human Neuroscience* 3, 70.
- Mathalon, D.H., Hoffman, R.E., Watson, T.D., Miller, R.M., Roach, B.J., Ford, J.M., 2010b. Neurophysiological distinction between schizophrenia and schizoaffective disorder. *Frontiers in Human Neuroscience* 3, 70.
- Näätänen, R., Paavilainen, P., Tiitinen, H., Jiang, D., Alho, K., 1993. Attention and mismatch negativity. *Psychophysiology* 30, 436–450.
- Näätänen, R., Simpson, M., Loveless, N.E., 1982. Stimulus deviance and evoked potentials. *Biological Psychology* 14, 53–98.
- Nuechterlein, K.H., 1977. Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. *Schizophrenia Bulletin* 3, 373–428.
- Oddy, B.W., Barry, R.J., Johnstone, S.J., Clarke, A.R., 2005. Removal of CNV effects from the N2 and P3 ERP components in a visual go/nogo task. *Journal of Psychophysiology* 19, 24–34.
- Pfefferbaum, A., Ford, J.M., White, P.M., Roth, W.T., 1989. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status and negative symptoms. *Archives of General Psychiatry* 46, 1035–1046.
- Picton, T.W., Hillyard, S.A., 1974. Human auditory evoked potentials. II: Effects of attention. *Electroencephalography and Clinical Neurophysiology* 36, 191–199.
- Pollux, P.M., Guo, K., 2009. Event-related potential correlates of spatiotemporal regularities in vision. *Neuroreport* 20, 525–530.
- Putnam, L.E., Roth, W.T., 1987. Automatic elicitation of cognitive components by startling stimuli. *Electroencephalography and Clinical Neurophysiology. Supplement* 40, 256–262.
- Remington, R.J., 1969. Analysis of sequential effects in choice reaction times. *Journal of Experimental Psychology* 82, 250–257.
- Reuter, B., Herzog, E., Endrass, T., Kathmann, N., 2006. Brain potentials indicate poor preparation for action in schizophrenia. *Psychophysiology* 43, 604–611.
- Rockstroh, B., Müller, M., Wagner, M., Cohen, R., Elbert, T., 1994. Event-related and motor responses to probes in a forewarned reaction time task in schizophrenic patients. *Schizophrenia Bulletin* 13, 23–34.
- Rohrbaugh, J.W., Syndulko, K., Lindsley, D.B., 1976. Brain wave components of the contingent negative variation in humans. *Science* 191, 1055–1057.
- Roth, W.T., Cannon, E.H., 1972. Some features of the auditory evoked response in schizophrenics. *Archives of General Psychiatry* 27, 466–471.
- Roth, W.T., Goodale, J., Pfefferbaum, A., 1991. Auditory event-related potentials and electrodermal activity in medicated and unmedicated schizophrenics. *Biological Psychiatry* 29, 585–599.
- Roth, W.T., Kopell, B.S., 1973. P 300—an orienting reaction in the human auditory evoked response. *Percept Mot Skills* 36, 219–225.
- Servan-Schreiber, D., Cohen, J.D., Steingard, S., 1996. Schizophrenic deficits in the processing of context—a test of a theoretical model. *Archives of General Psychiatry* 53, 1105–1112.
- Shelley, A.M., Grochowski, S., Lieberman, J.A., Javitt, D.C., 1996. Premature disinhibition of P3 generation in schizophrenia. *Biological Psychiatry* 39, 714–719.
- Simson, R., Vaughan Jr., H.G., Ritter, W., 1977. The scalp topography of potentials in auditory and visual Go/NoGo tasks. *Electroencephalogr Clin Neurophysiol* 43, 864–875.
- Spencer, K.M., Dien, J., Donchin, E., 2001. Spatiotemporal analysis of the late ERP responses to deviant stimuli. *Psychophysiology* 38, 343–358.
- Squires, K.C., Wickens, C., Squires, N.K., Donchin, E., 1976. The effect of stimulus sequence on the waveform of the cortical event-related potential. *Science* 193, 1142–1146.
- Squires, N.K., Squires, K.C., Hillyard, S.A., 1975. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography and Clinical Neurophysiology* 38, 387–401.
- Stadler, W., Klimesch, W., Pouthas, V., Ragot, R., 2006. Differential effects of the stimulus sequence on CNV and P300. *Brain Research* 1123, 157–167.
- Tueting, P., Sutton, S., Zubin, J., 1970. Quantitative evoked potential correlates of the probability of events. *Psychophysiology* 7, 385–394.
- Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophrenia Research* 76, 1–23.
- Umbricht, D.S., Bates, J.A., Lieberman, J.A., Kane, J.M., Javitt, D.C., 2006. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biological Psychiatry* 59, 762–772.
- van Boxtel, G.J., Brunia, C.H., 1994. Motor and non-motor components of the contingent negative variation. *International Journal of Psychophysiology* 17, 269–279.
- van den Bosch, R.J., 1983. Contingent negative variation and psychopathology: frontal-central distribution, and association with performance measures. *Biological Psychiatry* 18, 615–634.
- Verleger, R., Wascher, E., Arolt, V., Daase, C., Strohm, A., Kompf, D., 1999. Slow EEG potentials (contingent negative variation and post-imperative negative variation) in schizophrenia: their association to the present state and to Parkinsonian medication effects. *Clinical Neurophysiology* 110, 1175–1192.
- Wagner, M., Rendtorff, N., Kathmann, N., Engel, R.R., 1996. CNV, PINV and probe-evoked potentials in schizophrenics. *Electroencephalography and Clinical Neurophysiology* 98, 130–143.
- Walter, W.G., 1964. Slow potential waves in the human brain associated with expectancy, attention and decision. *Archiv für Psychiatrie und Nervenkrankheiten* 206, 309–322.